For reasons predicated on and intertwined with the Applicants' response to the Examiner's 35 USC §112, ¶2 rejections, below, the Applicants respectfully traverse the requirement to change the Abstract on the grounds that the Abstract *is* suitably descriptive of the claimed invention. The following emphasized language from the Abstract demonstrates why:

> This invention relates to genes which encode accessory molecule ligands *and their use for immunomodulation*, vaccination and treatments of various human diseases, including malignancies and autoimmune diseases. This invention also describes the use of accessory molecule ligands which are made up of various domains and subdomain portions of molecules derived from the tumor necrosis factor family. The chimeric molecules of this invention contain unique properties which lead to the stabilization of their activities and thus greater usefulness in the treatment of diseases. Vectors for expressing genes which encode the accessory molecule ligands of this invention are also disclosed.

Abstract (emphasis added).

The Applicants' position in this regard will be clearer from the discussion below.

Rejections under 35 USC §112

The Examiner has rejected claims 1-7, 67, and 83 for allegedly failing to describe "in such full, clear, concise, and exact terms as to enable any person skilled in the art to make and use the same, and/or for [allegedly] failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention." The Examiner focuses on the meaning of the claim term "ligand" and states that it is a relative term that is vague, unclear, and has an insufficient biochemical characterization (e.g., molecular weight, amino acid composition, N-terminal sequence, etc) for purposes of supporting the claims. The Examiner alleges that the term encompasses a "myriad of

molecules" that is not enabled and would lead to undue experimentation for one of skill in the art seeking to practice the claims.

While the term "ligand" can connote an inherent relativity and uncertainty when viewed alone, the Applicants respectfully submit that this is not the case here. The term "ligand" as used in the instant claims does not appear in, nor should it be construed in, a vacuum. Instead, the term's meaning as used in the claims should be read in its proper context—its relation to the proximate phrase, "accessory molecule," which combined has a clear and assigned meaning not only within the specification as written, but also within the art. The following specification passage illustrates this.

> *The accessory cell molecule ligand is only present on the activated T cells....*
>
> *When present on the surface of an activated T cell, the accessory ...[molecule] ligand can specifically bind to the accessory ... molecule present on the B cell...*
>
> The interaction with an activated T cell is not solely limited to B cells but rather *can be carried out by any cell which is able to present antigen to the T cell* (an antigen presenting cell). These cells include B lymphocyte, macrophages, dendritic cells, monocytes, Langerhans cells, interdigitating cells, follicular dendritic cells or Kupffer cells. *These cells all are known to have various accessory molecules on the cell surface which allow them to interact with other cells of the immune system.* For example, these antigen presenting cells all have the accessory molecule CD40 on their cell surface. *The presence of these accessory molecules allows these antigen presenting cells to specifically bind to complimentary accessory molecule ligand* and thus directly interact with *other* immune cells.

Specification, pg. 2, lines 33 et seq. (emphasis added).

An "accessory molecule ligand" is thus one that specifically binds an accessory molecule that is present on another or different cell type--an intercellular reaction. This epitomizes the utility of the invention—converting a normally intercellular event to an intracellular one through supply and expression of a cognate accessory molecule ligand gene in the same cell that expresses the complementary accessory molecule.

The very art cited by the Examiner in the Office Action supports this point. For example, the Examiner cites Alderson et al. (1993) J. Exp. Med. vol. 178, pp. 669-674. Alderson clearly delineates and distinguishes accessory molecule ligands from cognate accessory molecules:

> CD40 is…expressed on B cells….[F]orms of a ligand for CD40 (CD40L) were recently cloned and demonstrated to be…expressed primarily on activated…T cells…

Alderson, pg. 1, ¶1.

The reference, Yellin et al (1994,) also supports the Applicants' position:

> An important component of T cell help for B lymphocyte differentiation is the *contact-dependent signaling mediated by the T cell-B cell activating molecule (T-BAM/CD40-L), and activation-induced surface membrane protein on CD4+ T helper cells in lymphoid follicles that interacts with the B cell surface molecule, CD40.*

Yellin, Abstract, (emphasis added).

The Freeman '310 patent is also consistent with this understanding.

> A costimulatory molecule…has been identified on B cells and other APCs… Binding …[of this molecule] to a ligand on the surface of T cells provides costimulation to the T cell.

'310 patent, column 1, lines 49-55.

It is thus clear from the Applicants' specification and the art cited by the Examiner that the term "ligand," when juxtaposed to such terms as "accessory molecule" or "costimulatory molecule," has a very definite, distinct and well-known meaning in the art. The Examiner's contrary position is therefore respectfully traversed.

Viewed in the above light, the Examiner's contention that the claimed invention is not enabled is also respectfully traversed. As discussed, the clear meaning assigned to the term "accessory molecule ligand" substantially narrows the universe of possible ligand types.

The Examiner correctly notes the standard—"that there must be a reasonable correlation between the scope of the claims and scope of enablement set forth." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24, (CCPA 1970). Nevertheless, the Examiner misapplies this standard in concluding that undue experimentation would be required in order for one of ordinary skill in the art to practice the invention. As demonstrated below, consideration of all the factors discussed in the seminal enablement case of In re Wands, 858 F.2d 731m 8 U.S.P.Q2d 1400 (Fed. Cir. 1988) demonstrates that the invention as claimed *is* enabled.

The court in In re Wands specified eight factors to be considered in determining whether a claimed invention is enabled: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Examiner overstates the experimentation required to practice the instant claims. The identification and isolation of nucleic acids encoding accessory molecule ligands and their subsequent introduction into appropriate human cells so that they are functionally co-expressed with corresponding cognate accessory molecules requires no more than routine experimentation. As the Examiner has already duly noted on page 3 of the Action, and as aptly demonstrated in the specification at pages 4 and 31, the TNF family of genes and gene products is already well characterized, thus considerably reducing the need for experimentation.

> A large number of accessory molecule ligands are members of the tumor necrosis factor superfamily. (Fanslow et al., Sem. Immun., 6:267-268 (1994). *The genes for a number of these accessory molecule ligands have been cloned and identified. These accessory molecule ligand genes encode accessory molecules which all have the configuration of Type II membrane proteins and exhibit varying degrees of homology with other accessory molecule ligand genes.* For example, the accessory molecule ligand genes encoding both murine CD40 ligand and human CD40 ligand have been isolated. See, Armitage et al., Nature, 357:80-82 (1992) and Hollenbaugh et al., EMBO J., 11:4313-4321 (1992).

Specification, pg. 4, lines 1-13 (emphasis added).

By using degenerate oligo probes, one can fish out corresponding cDNAs or genomic sequences harboring novel ligand genes and quickly deduce sequence and function. One can

then conveniently manipulate such genes so that they will be functional in a given transfected cell type—e.g., by operationally affixing them to constitutive or inducible promoters and/or other regulatory elements. These elements may be part of a viral, plasmid, or other vector that can be conveniently introduced into human cells so as to alter immunoreactivity as claimed. What the art does not teach as to the specific therapeutics of the invention is supplemented by the application as written. Otherwise, the molecular techniques required are all fairly routine and predictable. Factors 1, 4, 5, and 7 of Wands thus favor enablement.

Wands factors 2 and 3 further support enablement. Factor two is the amount of direction or guidance supplied in the application. Factor three is the presence or absence of working examples. The Applicants give two detailed working examples—one for FASL (Example 5, pg. 98 et seq.) and one for CD40L (Example 1, pg. 63 et seq.). The Applicants thus satisfy both of these factors as required under Wands.

Factor 5, the skill level in the art, is high and therefore also favors enablement of the claimed invention.

The final factor, breadth of the claims, also inures to the Applicants' favor in light of the other factors already noted which suggest that the claims' scope *is* fully enabled. This is especially so in light of various Federal Circuit pronouncements governing enablement. For example,

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

PPG Industries, Inc. v. Guardian Industries Corp., 75 F.3d 1558, 37 U.S.P.Q.2d 1618 (Fed. Cir. 1996) (citing Ex Parte Jackson, 217 U.S.P.Q. 804, 807 (1982)).

And,

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.

In re Certain Limited-Charge Cell Culture Microcarriers, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985).

In light of the above, the Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection of the claims.

Rejections under 35 USC §§ 102 and 103

The Examiner has rejected claims 1-8, 10 and 83 over 35 USC §102(b) as allegedly anticipated by Yellin et al. (J. Immun., 1994). The Examiner states that Yellin teaches that "transfecting cells, including leukemia cells, with CD40 ligand enhances a cell costimulatory activity." However, this is incorrect.

Yellin shows CD40-L specific effects on B cell isotype secretion mediated by supply of CD40-L signals to an entirely different cell type (CD40-L^+ Jurkat T cell lymphoma D1.1). Yellin, pg. 2166, col 2, ¶ 2. The Applicant has thoroughly read and fails to note any mention of transfection in this reference, let alone the precise parameters of the Applicants' invention. Yellin hence does not teach what the Applicants teach.

The Examiner has also rejected claims 1-10, and 83 under 35 USC §102(b) over Alderson et al. (J. Exp. Med., 1993) stating: "Alderson et al. teach that CD40 ligand transfected cells induce monocytes to become tumoricidal" and "transfection with either murine or human CD40 ligand." However, the Applicants' reading of Alderson does not show transfection of a *human* cell line as required by each of Applicants' claims 1-10, and 83. Alderson instead teaches transfection of cell line CV-1, which is a monkey, and not a human, cell line. Furthermore, Alderson teaches cellular adhesion of monocyte cells and tumoricidal induction of the same by contact with transfected cells of an entirely different origin. Pg. 671. Alderson thus teaches intercellular effects and applications, and not the initial intracellular signaling that Applicants' claims teach.

Finally, claims 1-7, 67 and 83 are rejected under35 USC §102(e) over US Patent 5,861,310 ("the '310 patent") issued to Freeman. The Examiner states that "Freeman et al. teach altering the reactivity of a cell...by introducing a gene encoding an accessory molecule ligand (B7) alone or together, that is to be expressed on the cell surface."

The Applicants have carefully read the '310 patent in its entirety and cannot confirm or accept the Examiner's characterization of that reference. Freeman teaches transgenic supply of B or APC cell accessory molecules (B7, B7-2, and B7-3), and not corresponding ligands (e.g., CD28 and CTLA-4). As stated earlier, these two species of molecules are clearly delineated and distinguishable within the art. The claimed invention is thus different from the '310 patent's teachings.

In light of above clarification of the claims over the cited art, the Applicants respectfully submit that patentable differences over the art exist that warrant withdrawal of the stated rejections. This applies not only to the rejections founded on §102 grounds, but also to those rejections founded on §103 grounds as well. The references' combined teachings in no way teach or suggest the claimed invention, and therefore do not amount to legal obviousness. To capitulate, the references teach transfection of cells with genes that encode accessory molecules that are characteristic of *normal expression in those very cell types*. The Applicants' invention is different in that it teaches the useful transfection of (accessory molecule ligand) genes that are not normally or functionally expressed in cells which express the corresponding and complementary accessory molecules. As noted above, the art and the specification communicate a clear distinction between accessory molecules and accessory molecule ligands.

Conclusion

For the forgoing reasons, it is respectfully submitted that the claims as written are clear, enabled, and not anticipated nor rendered obvious by any of the references cited. It is therefore respectfully requested that such grounds of denial for a patent on the subject claims be withdrawn.

Respectfully submitted,
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